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1. Your reference

02P064

2. Patent application number
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0228826.4

11 DEC 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

(1) JOSEPH OKPALA and EL HASSANE (2) LARHRIB respectively of Flat 1, 18 Huskisson Street, Toxteth, Liverpool L8 7LR and 38, Eirle Road, Liverpool L7 6HF, United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

(1) 8524787001 (2) 8524811001

4. Title of the invention

HAIR TECHNOLOGY IN CREATING PARTICLES WITH IMPROVED DELIVERY CAPABILITIES

5. Name of your agent *(if you have one)*

POTTS, KERR & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

15 Hamilton Square
Birkenhead
Merseyside
CH41 6BR, United Kingdom

Patents ADP number *(if you know it)*

1313002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
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Claim(s)	
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Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature: Patts, Kerr & Co

Date: 10 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Paul A. Thomson 0151 647 6746

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HAIR TECHNOLOGY IN CREATING PARTICLES WITH IMPROVED DELIVERY CAPABILITIES.

Field of the Invention

The invention relates generally to the field of selectively modifying the morphological features of particles to improve effective delivery to a target region. In particular, the invention relates to the modification of particles for delivery via inhalation.

Background of the invention

In most Dry Powder Inhalers (DPI's) drug particles for delivery to the lower alveoli regions of the lung need to be of the size range 1- 5 micrometers. Unfortunately particles of this size range are rarely crystallised directly, instead, they are normally produced by milling. This latter processing causes uncontrollable degrees of disruption to the crystal surface leading to a product which is highly charged, cohesive and difficult to process.

Spray drying has been seen as an alternative technique as the shape of the particle can be easily controlled whilst producing particles with a narrow size distribution. However, the particles produced are always cohesive and suffer from poor flow and hence cannot be realistically aerosolized . The poor processing properties of the drugs obtained by the above techniques, coupled with low therapeutic dose, necessitate the addition of a carrier to improve processing and drug aerosolization. These conventional formulations composed of a binary blend (carrier / micronised drug, typically 67.5 to 1 w/w) struggled to achieve lung drug depositions of 15%, this is discussed in more detail in *Shekunov and York, J. of Crystal Growth, 211(2000),122-136, Lorgström, L., Derom, E., Ståhl, E., Wåhlin-boll, E. and Pauwels, R., Am. J. Respir. Crit. Care Med, Vol 153, pp 1636-1640, 1996.*

Improvements have been obtained in delivering the drug to the lower airways by lowering the density of the drug particles (*See references Edwards et al, Science, 276 (5320), 1868-1871, 1997, Vanbever et al., 1999, Bosquillon et al, 2001, Ben-Jebra et al 1999*). The lower density and larger size of the particles allow them to be aerosolized easier and disperse easily

within the air stream allowing more drug particles to deposit in the lower airways and this was purely due to the improvements in their aerodynamic properties. In *US patent 6,284,282* drug lung depositions in excess of 40% of the administered dose were achieved using carrier / drug ratios of 10 to 1 w/w. This is strikingly superior to the conventional formulations (i.e. carrier / micronised drug). The engineered low density drug particle can aerosolize easily from the inhaler device; as a result less carrier is required. The improvements made come at a price in that typically 4 – 5% of the drug was included in a multi-component system. Such complex systems increase the possibility of physical incompatibilities between components and may be undesirable in terms of patient acceptability. In addition these complex systems will be slow release in origin resulting from the use of polymeric matrix and lipid / waxy based excipients. This is unacceptable in treating acute respiratory conditions.

From the above, it is obvious that improvements in the drug particle properties improves drug lung deposition. Since the drug is always necessarily mixed with the carrier, improvements in the carrier should also improve drug deposition.

The carrier is often obtained by crude uncontrolled crystallisation from various solvents but significant amounts of material and solvent are wasted. After crystallization, the crystalline carrier is harvested, dried, sieved and comminuted if required. Due to the nature of manufacture the carrier tends to be dense and is of unpredictable shape and surface properties thus leading to batch to batch variations in drug deposition.

The surface of the carrier particle is not usually smooth but it has areas of roughness (asperities and clefts). The sites of an asperity and cleft are believed to be regions of high surface energy. The drug particles are preferentially attracted to, and adhere more strongly to, these high energy sites. Consequently, the detachment of drug particles from these sites, upon inhalation, is reduced and uneven, ultimately resulting in unpredictable and reduced deposition of the aerosolised drug particles.

It is advantageous to reduce the number of these high energy sites available for the drug particle to adhere. In *US patent 6,153,224* this was achieved by the addition of an anti-adherent material, which reduced carrier drug adhesion. The respirable fraction of the drug achieved was as high as 40% Addition of a fine carrier to occupy the high energy sites of the coarse

carrier, followed by admixture of the drug, improved drug deposition from 6.3% to 13.4 % (*See reference Tee et al, 1999, Proceedings of Drug delivery to the Lungs X, 33-36*). However, the disadvantages of ternary mixes include difficulties in selecting the appropriate process of milling to generate fine carrier, the type of fine carrier employed, and the sequence and time of mixing. All of which will have an impact on drug content uniformity. *US Patent 5,376,386* disclosed a process of producing smooth carrier particles by crystallization from aqueous medium. The resulting particles improved drug deposition.

In reference Larhrib et al, 2000, Proceedings of Drug delivery to the Lungs XI, 18-21 the Engineering of elongated carrier particles was shown to improve the deposition of Salbutamol sulphate from 5.5% to 22%. However, the formulation containing elongated carrier particles produced lower and inconsistent emissions of Salbutamol sulphate from the inhaler device. This was attributed to the poor flow properties of the engineered elongated carrier.

The carrier is always present in a much higher concentration than the drug. Thus, despite improvements made in the drug particle design, the overwhelming presence of the carrier will dilute and reduce any drug particle improvements made. However, improving the carrier particle design, in order to reduce carrier / drug ratios and promote carrier and drug aerosolization coupled with improved drug particle design, will ultimately increase lung drug deposition. Despite the efforts by various researchers in modifying the carrier particles the deposition is in general much lower than that obtained by engineering the drug particles.

The prior art teaches the design or use of high density carrier, such that it will remain in the inhaler device or impact in the mouth or back of the throat so that the drug alone is detached and deposit in the lower airways. Large carrier particles will achieve these requirements.

Furthermore, the strong adhesion between the drug and dense carrier resulting from the surface roughness and/or presence of crevices on the surface of the carrier, further impedes drug detachment. Thus increasing the amount of the drug particles impacting at the site of the carrier. Even where there is weak adhesion between drug and carrier, since the carrier impacts rapidly due to its high inertia, the drug has insufficient time to detach before

impaction of the carrier. There are thus two important issues in the teaching of the prior art:

1) High density carrier
2) Smoothing the surface of the carrier

It is an object of this invention to provide carrier and or drugs with or without rough surfaces which are of low density. The drug processed in the way of this invention can also act as a carrier for other drug(s) or additive(s).

The present invention is contrary to the prior art, where rough surfaces have been seen as a burden for traditional dry powder inhalation, such rough surfaces in this invention are advantageous (see below). In fact the present invention seeks to promote roughness of the particle surface (or asperities) by the presence of projections (hairs) and/or pores.

The present invention also teaches that extra benefit can be gained by increasing the hollow volume of the particles, and thus decreasing the particle density.

The low density of the particles caused by the hollow volume and the presence of pores on the surface impart excellent aerodynamic properties of the particles, allowing them to be aerosolized with a minimum inhalation effort from any given inhaler device and the emitted particles will travel further in the air stream despite changes in air stream velocity.

The regular shape coupled with low density of the carrier allows better technical handling and easier and total aerosolisation of the powder. The regular spherical shape flows better allowing consistent filling of the blister compartment or gelatin capsules and also better emptying during inhalation.

The low density of the carrier facilitates a long flight time which in turn allows more drug particles to detach (with those that are unable to detach impacting much further down within the lung structure) compared with the traditional high density carrier, which usually remains in the inhaler device or impacts in the mouth.

Summary of the Invention

The present invention provides a method of producing particles with modified morphology, which provide improved delivery wherein the method comprises: a) processing at least one substance alone, or at least one additive alone or combinations of said substance(s) and additive(s) to form hollow particles; b) contacting said particles with a fluid which contains at least one agent, which is capable of forming, enhancing or modifying features of the particles morphology; c) harvesting and drying the resultant particles.

Preferably, the features of the morphology that are created and/or modified in this method are surface projections (hairs), pores, spongy formation and hollow volume.

Preferably, the particles are substantially spherical in shape.

Preferably the agent may be a substance, as defined herein, or an additive, as defined herein.

The term ''substance'' is to be understood as incorporating therapeutic, prophylactic and diagnostic agents, or excipients suitable for use in the pharmaceutical field. However, other materials commonly used in pharmaceutical compositions, such as diluents, flavourants, fragrances, dyes, sweetners and other agents that are compatible are also encompassed within the present invention. The application of the present invention outside of the pharmaceutical arena are also envisaged.

Furthermore, the therapeutic, prophylactic or diagnostic agent of this invention can be but are not limited to peptides, proteins, organic, inorganic substances, pro-drugs, antigens, hormones and the like.

The term '' additive'' is taken to include any matter in any physical state which has particle morphology modifying properties.

An additive includes any non-substance that can be used to promulgate or modify projections (hairs) and/or pore formation. The additive can be used

to modify the physical, chemical and/or biological properties of a substance thereby facilitating the technical handling, improving the stability of the said substances, it can also affect the mechanical properties of the resulting substance or substances and/or influencing the biological response of the said substances.

Environmental additives include heat, moisture, radiation, pressure, shear forces, magnetic forces, vibration, systems of agitation, stirring, vortexing, centrifuging, masticating, ultra-sound waves or extruding, electrical or any factors or combinations of factors that favour the formation of hairs and/or pores and/or physico-chemical modification.

Preferably, the drying can be achieved by any process which is not limited to air, conventional oven, vacuum oven, fluid bed dryer, freeze dryer and any other technique employed to remove fluids from a powder.

It is appreciated that drug particles engineered according to the present invention can be used as a carrier for other particles, which may be another drug. This is advantageous, in that one or more drugs can be introduced and aerosolized from the same inhaler device. This should improve patient compliance whilst minimizing costs.

The concept can also be applied to engineering one particle composed of two or more drug substances alone or combined with additive(s). The additive(s) may even be a carrier for inhalation, flavouring agents, taste masking agents and the like.

Thus, the concept of particle engineering according to further embodiment of the present invention can be extended to the design of a formulation composed of several components, within one particle, with desirable properties and for any intended use. This is technologically, economically and therapeutically advantageous.

The term "fluid" is defined herein as the medium or combination of mediums in which partial or complete architecturing of the particle takes place. Complete architecturing is defined herein as obtaining particles with the physico-chemical properties for the intended purpose. Partial architecturing is defined herein as obtaining particles with physico-chemical

properties anywhere between those of complete architecturing and that of the original particle. The original particle in this instance is the particle before contacting. The constituent and medium defined herein is a substance and/or additive. One or more substance(s) and/or additive(s) of the particle can be present as one or more constituents of the fluid before contacting and or during contacting. The fluid may also contain substance(s) and/or additives as constituents which are not present in the particle.

There are many physico-chemical properties which can be altered to enhance the usefulness of a particle, they include but not limited to: size, shape, surface texture, crystallinity, mechanical properties (i.e, friability, tensile strength, elastic, brittle, plastic, glassy and rubbery states or combinations thereof), polymorphism, solubility, dissolution rate, specific surface area, density, aerodynamic properties, hygroscopicity, adhesive and cohesive forces and combination thereof.

Further important physico-chemical properties, which can be affected to increase the usefulness of the particles, include: the particle's flow properties, hollow volume and porosity, as well as the size and shape of the pores.

In the language of the invention the term '' hair'' will be understood to describe any projection from a particle, that is between 0.001 and 5000 micrometers in length.

Important physico-chemical properties of the hairs, which can be affected to increase the usefulness of the particles, include the type, nature of the substance(s) and/or the additive(s) composing them and the number, surface density, direction of growth and the rate of growth.

There is no restriction on the type of material forming hairs, enabling instantaneous, controlled or sustained release profiles, in order to suit the intended use. The hairs can be produced from a suitable and safe (generally recognized as safe ''GRAS'') penetrating enhancer agent to achieve the intended pharmacological effect of the active ingredient.

The nature, quantity, the length and the physico-chemical properties of the hairs can be engineered in a controlled fashion to suit the intended use, to

give for example increasing specific surface area, thus more drug can be loaded onto the hairs reducing the quantity of carrier required compared to the conventional carrier.

The presence of hairs maintain the stability and content uniformity of the mix. The hairs also minimise the contact between the carrier particle core and the drug, hence, weak adhesion between the drug and carrier results. The hairs are part of the carrier, however, they act as a ternary component preventing full contact between the carrier core and the drug. This is a new concept contrary to the prior art, where a ternary component (such as fine carrier) is added to reduce the adhesion between the drug and carrier. The density of the hairs can be adjusted to enable the hairs to oscillate or vibrate when the particles are subjected to the inhalation flow rate. Low adhesion of drug particles to the hairs combined with efficient oscillation of the hairs allow better detachment of the drug particles, the remaining drug particles attached to the hairs and/or to the carrier core will travel with the low density carrier.

Furthermore, the hairs can be produced from a bioadhesive excipient which at point of carrier impaction allow the hairs to act as grappling hooks anchoring the carrier-drug particles or drug particles to the impact site of the lung epithelia allowing the drug to be released and absorbed. This concept is important for delivering very small particles below 0.5 micrometer such as liposomes to the lung, this particle size range is known to be cleared from the lung, whereas the presence of hairs will maintain them at the impact site until they have released their pay load. Hence the presence of hairs will maintain particles lower than 0.5 micometers at the impaction site, preventing their expiration or muco-cilliary clearance. Such small particles are pharmacologically advantageous as their large surface area to volume ratios give superior and faster absorption. These small size ranges are thus made pharmacologically useful with this technology whilst in traditional formulations these size ranges are usually cleared.

Liposomes or nano-particles are usually made from waxy materials such as surfactants and are consequently delivered by wet nebulisation but never by dry powder aerosilation using conventional technologies, carrier or prior art. This is due the high liposome- liposome (or nano-particle – nano-particle) cohesion and adhesion forces, however, these high adhesive forces are unimportant with this new invention as the whole (i.e light hairy carrier particle and lipsome or light hairy carrier and nano-particle) is delivered to

deep lung. Liposomes are ideal carrier systems in that they are hydrophobic, which will be quickly and easily absorbed and transported by the hydrophobic lung epithelia. Liposomes, generally, are usually opsonised or phagocytised hence they have a short biological half life. Application of this process to produce hairs on the surface of liposomes increases their biological half lives and hence improves their pharmacological usefulness.

The size of the carrier can be controlled predictably compared to the traditional teaching of crystallization, with high degree of uniformity and monodispersity. Since the carrier has excellent aerodynamic properties, then the drug to be formulated with the carrier can be either micronised or engineered, but in all cases excellent deposition in the lower airways is achieved.

It will be appreciated that, just as the usefulness of the carrier particles can be improved by selective architecturing, as with carrier particles the drug itself can also be engineered, using the same process, thereby permitting the drug to be aerosolised on its own; or with a traditional carrier; or with engineered hairy/porous/hollow carriers.

The few examples given above were used to clarify and highlight the utility and the importance of the hairy particles, these are not limiting examples, but the particles and or hairs composing them can be engineered to achieve the technological and biopharmaceutical goals and for any route of drug delivery.

Previously, it was stated that the carrier could be designed with morphological features which actively promote drug detachment from the carrier. One such morphological feature has been commented in US patent 5,869,098, however, the author's failed to realise it's importance. It was used in this patent purely as a reference to indicate the cessation of crystallization. However this invention is specific in actively seeking to produce this feature as one of the important and integral parts of the engineered particles. This feature as described, *US patent 5,869,098* is " fine cat whisker-like needles and tiny blades which grow and project along the surface"

Although the present invention shares one technique, that is immersion of solids in solvents, with *US patent 5,869,098*, the aim and resultant product is completely different and possess several advantages compared to *US patent 5,869,098.*

The principle events in *US patent 5,869,098* are
1 production of floss using high temperature and high shear forces
2 Chopping of the floss
3 Addition of additive, which may be bioactive that may act as a nucleating agent.
4 Immersion or addition of organic solvent (with or with out the presence of water), or subjection of the floss to organic solvent vapour, with the intention of producing a crystalline material.
5 The final recovered product is in the form of spheriodal micro-crystallites which essentially consist of agglomerated rods in the form of a "dome or raspberry like structure".
6 The product is aimed as a fondant comestible.
7 Suggest the use of the resultant particles as inhalants

For the present invention, addressing items 1-7 above.

A floss is not produced, in fact the starting material need not even be processed but can be used in the raw state. Contrary to *US patent 5,869,098*, the starting material for this invention is not limited to those that are amorphous, crystalline materials can also be processed with the same results. There is also no limitation on the starting shape or size. The floss is amorphous in nature and consequently is thermodynamically unstable hence it was necessary to process it at comparatively low temperatures otherwise it's structural integrity was destroyed. Processing the floss at elevated temperature will ultimately lead to uncontrollable crystallization and floss destruction. Whereas, in this present invention the application of heat is desirable, in that it reduced the processing time, it facilitated pore and hair forming processes whilst increasing internal hollow volume and pore size. In addition the solid nature of the starting material is more resistant to elevated temperatures compared to the floss and the elevated temperature enabled the starting material to grow in an isometric manner, whilst maintaining it's high degree of mono-dispersity and maintaining the shape of the original particle.

Since the floss is made from sugars, this limits the starting materials to sugars. The spheriodal micro-crystallites are not true spheres but agglomerates of rod like crystals. Whereas, the present invention retains the original shape of the starting material. Since the final product of *US patent 5,869,098* is much denser than the starting floss these particles may be undesirable for inhalation as light particles are required (as discussed above). In addition for inhalation, these micro-crystallites must disperse in the inhaler device and given the fact that this dispersion occurs in saturated sugar solutions, this would be difficult to obtain in an inhaler device in the dry state. Furthermore the rough surface characteristics of the micro-crystallites would impede drug detachment. All of these limit the use of such particles in dry powder inhaler devices. The present invention produces aerodynamically favourable particles with low bulk density that can be delivered as a whole to deep lung rather than as fragments (*US patent 5,869, 098*). In addition the present invention can deliver the drug alone without the need of a carrier, whilst *US patent 5,869, 098* needs re-crystallised floss as carrier.

US patent 5,869,098 whilst re-crystallising amorphous material increases it's bulk density and lowers the corresponding specific surface area. In contrast, the present invention increases the specific surface area and decreases the bulk density. Furthermore, the hairs produced by the present invention extend outwards, as if from the center of the particle whilst that of *US patent 5,869,098* the solid crystallite rods are at right angles to the circumference of the spheroid. Also in the present invention the number, size the density and other characteristics of the hairs can be manipulated to achieve the requirements for that application.

Detailed Description

1. A method of selectively architecturing particles with special morphological features including but are not limited to hairs, spongy-form, porous and combinations thereof for inhalation or any other pharmaceutical and non-pharmaceutical uses, where these particles are deemed desirable. The use of these particles includes but is not limited to use as a whole, as fragments of any size, 'de-haired' whole particles, 'de-haired' fragments of any size, hairs alone or combinations thereof. Further modifications of said particles, or morphological features and production of said morphological

features in improving the compositions in which they are included is also embodied within this invention.

The hairy and or porous particles and formulations containing them, can be given by different administration routes, such as, but not limited to, the oral, the parenteral, the nasal, the pulmonary, the rectal, the tonsillar, the buccal, the intraocular, the topical/transdermal, the vaginal etc, intended for local, regional, and/or systemic effects. The preferred administrations are by the oral, nasal, pulmonary and rectal routes.

2. A method for architecturing particles, this method comprises : contacting substance(s) with or without additive(s) or additive(s) alone with a fluid to produce particles with hairs and or pores alone with or without modifications to the physico-chemical properties (not limited to those physico-chemical properties detailed in detailed descriptions 3, 4 and 5) of the resulting particle from that of the original particle, in order to produce suitable particles for the intended use.

3. According to detailed description 2, wherein physico-chemical properties are suitable for the intended use and include: the size, shape, surface texture, crystallinity, mechanical properties (i.e., friability, tensile strength, elastic, brittle, plastic, glassy and rubbery states or combinations thereof), polymorphism, solubility, dissolution rate, specific surface area, density, aerodynamic properties, hygroscopicity, adhesive and cohesive forces and combinations thereof.

4. According to detailed descriptions 2 and 3, wherein other physico-chemical properties of the particle include the type and nature of the substance(s) and / or additive(s) comprising the particle, it's flow properties, hollow volume and porosity, size and shape of the pores.

5. According to detailed descriptions 2, 3 and 4, wherein other physico-chemical properties of the hairs include the type, nature of the substance(s) and / or the additive(s) composing them and the number, surface density, direction of growth and the rate of growth.

5.1 According to detailed description 5, wherein hairs are defined herein, as any projections from the surface of the particles, of any length, preferably from 0.001 micrometers to 5000 micrometers and in any direction to the surface of the particles.

6. Architecturing according to detailed description 1, means creating and or enhancing and or modifying hairs and pores and/or modifying the physico-chemical properties of the particles and/or hairs to suit both technical and bio-pharmaceutical requirements in order to achieve successful therapy.

7. The following general steps in the procedure for forming hairy and / or porous particles are further exemplified in the experimental section below:
   a) Processing substance(s) alone, additive(s) alone or combination(s) of substance(s) and additive(s) to preferably form hollow spherical particles. The particles to be contacted can be in any state of matter (as detailed in detail description 7.1), preferably the solid state or frozen state.
   b) Contacting said particles with one or more agents which form, and/or enhances and or modify hairs. These agent(s) can also form and or enhance and/or modify existing pores. These agent(s) can also form and/or promote and/or modify spongy form particles. These agents can also form and/or enhance and/or modify the hollow volume of the particle. An agent in this instance is a substance or additive (see later).
   c) Allowing spongy-form, and/or hair formation and/or porousness and/or changes in the physico-chemical properties of particles and/or hairs as detailed in detail descriptions 3, 4, 5 to the extent required.
   d) Repeating steps a) to c) as many times as required.
   e) Harvesting and drying the resulting particles.

   Repeating steps a) to e) as many times as required.

Drying can be achieved by any process which is not limited to air, conventional oven, vacuum oven thermally or isothermally with or without change in pressure, fluid bed dryer, freeze dryer and any other technique employed to remove fluid(s) from a powder.

The substance or substances, additive or additives or combinations thereof, can be added in any physical state of matter as described in detailed description 7.1, at any stage in the processes a to f above.

7.1 State of matter as used herein includes but is not limited to solid, liquid, gas (ideal, real or mixtures thereof), vapour, supercritical fluids, solutions, suspensions, dispersions, emulsions or micro-emulsion, colloids, liquid crystals, visco-elastic, gels, slurry, paste, semi-solid, molten and combinations thereof.

8 The substance as defined herein is selected from the group consisting of therapeutic, prophylactic, diagnostic agents or excipient(s) suitable for use in the pharmaceutical field, although other materials commonly used in pharmaceutical compositions, such as diluents, flavourants, fragrances, dyes, sweetners and other agents that are compatible are also encompassed within the present invention. Utilities outside of the pharmaceutical arena are also envisaged. Compatible in this instance means that they are pharmaceutically acceptable or "generally recognized as safe" (GRAS) for delivery to the human and animals and also can act as hair, and/or pore forming and/or promoting and/or changes in the physico-chemical properties (of hairs and/or particles) as described in detailed descriptions 3, 4 and 5. Agent (s) are defined in this instance as substance(s) or additive(s).

Herein a therapeutic, prophylactic or diagnostic agent is a substance which has biological / pharmacological activity. An excipient is a substance selected from the group of sugars. Sugars are those substances which are based on simple crystalline (but are not limited to) monosaccharide, disaccharide, polysaccharide structures and sugar alcohols such as sorbitol, mannitol, maltitol, etc. The sugar of choice in the present invention is lactose.

Herein the therapeutic, prophylactic or diagnostic agent of this invention can be but are not limited to peptides, proteins, organic substances, inorganic substances, pro-drugs, antigens, hormones and the like.

Furthermore the substance can be but are not limited to proteins, lipids, nucleic acid, short-chain peptides, corticosteroids, anti-inflammatories e.g. beclomethasone, betamethasone, fluticasone, flunisolide, budesonide, dexamethasone, tipredane, triamcinolone acetonide, anti-tussives e.g. noscarpine, bronchodilators e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, formoterol, terbutaline, isoetharine, tulobuterol, orciprenaline or (-)-4-amino-3,5-dichloro-α[[[6-[2-(2 pyridinyl)ethoxy}hexyl]amino]methyl]benzenemethanol, diuretics e.g. amiloride, anticholinergics e.g. ipratropium, ipatropium bromide, atropine, oxitropium or oxitropium bromide, hormones e.g. cortisone, hydrocortisone or prednisolone, xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline, analgesics e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine, anginal preparations e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromyl, anti-infectives e.g. cephalosporin, penicillins, streptomycin, sulphonamides, tetracyclines or pentamidines, anti-histamines e.g. methapyrilene; anti-neoplastic agents e.g. bleomycin, carboplatin, methotrexate and adriamycin, amphotericin B, anti-tuberculous agents e.g. isoniazide or ethanbutol, therapeutic proteins and peptides e.g. insulin or glucagon, prostaglandins and leukotrienes and their activators and inhibitors including prostacyclin (epoprostanol), and prostaglandins E_1 and E_2 and any other agents that can be delivered to the lungs for topical, systemic, controlled sustained release effect. It will be apparent to the skilled artisan that, where appropriate, the therapeutic agents may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimize the activity and/or stability of the therapeutic agent. A preferred therapeutic agent is selected from the group consisting of anti-inflammatories and bronchodilators. Particularly preferred therapeutic agents are beclomethasone dipropionate and salbutamol sulphate.

In another embodiment of the invention, nutrients can be used and include but are not limited to retinoids e.g. all-cis retinoic acid, 13-trans retinoic acid and other vitamin A and beta carotene derivatives, vitamins D,E,K and water insoluble precursors and derivatives thereof. Therapeutic agents may be selected from suitable combinations of the therapeutic agents mentioned hererinbefore. In a preferred embodiment, combinations comprise a short acting β_2 agonist + antimuscarinic e.g. salbutamol + ipatropium bromide; or fenoterol + ipatropium bromide. Short acting β_2 agonist + corticosteroid e.g.

salbutamol + beclomethasone. Long acting β_2 agonist + corticosteroid e.g. salmeterol + fluticasone; or eformoterol + budesonide.

In another embodiment substance or substances might contain one or more therapeutic, prophylactic or diagnostic agents and their mixtures thereof, alone or in combination with one or more pharmaceutical excipients. For example, the excipient may be a non-biodegradable or biodegradable or bioerodible polymers, in order to achieve a retarded, controlled, sustained or targeted release system of the therapeutic, prophylactic or diagnostic agent. The term biodegradable or bioerodible as described herein means a polymer that chemically or enzymatically degrades in vivo to small non-toxic molecules. Suitable polymers for the above applications can be synthetic or natural of origin, can include but are not limited to cyclodextrins and derivatives thereof, sodium caseinate, dipalmitoyl phosphatidyl choline (DPPC), human serum albumin, phospholipids cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, ethyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, methyl cellulose, cellulose acetate butyrate, poloxamer ,poly(lactic acid), poly(lactic-co-glycolic acid), poly(lactide)s, poly(glycolide)s, poly(lactide-coglycolide)s, poly(p-dioxanones), poly(caprolactone), polycarbonates, polyamides, polyanhydrides, poly(alkylene alkylate)s, polyamino acids, polyhydroxyalkanoates, polypropylenefumarates, polyorthoesters, polyacetals, polyacrylamides, polycyanoacrylates, polyalkylcyanoacrylates, polymethapolyphosphate esters, polyphosphazene, polyurethanes, polyacrylates, polymethacrylate, poly(methyl methacrylate), poly(hydroxy ethyl methacrylate - co methyl methacrylate), carbopol 934, etc., ethylene-vinyl acetate and other acyl substituted cellulose acetates and derivatives thereof, polystyrenes, polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonated polyolefins, polyethylene, polyethylene glycols, polypropylene, polyethylene oxide, copolymers and blends thereof. Preferably, the selected polymer is biocompatible in that it degrades or erode in-vivo to form non-toxic small molecules. More preferably, the biocompatible polymer is pharmaceutically acceptable for delivery to the respiratory tract. Even more preferably, the polymer is both pharmaceutically acceptable to the lung and has therapeutic properties. In the latter embodiment, suitable polymer candidates include cellulose acetate phthalate or hydroxypropyl cellulose acetate phthalate, polymeric drugs or genetically-engineered polymers.

The substance or substances to be treated might contain one or more stabilizers to protect the therapeutic agent from degradation and maintain the biological activity. The term stabilizers as described herein means any agent which binds or interacts in a covalent or a non-covalent manner with the therapeutic, prophylactic, diagnostic agent or excipient. Suitable stabilizers that can be used in the present invention are described in other patents (see for instance US 5,716,644; 5,674534; 5,654,010, 5,711,968; 6,284,283). In a preferred embodiment, the stabilizing agent for the therapeutic agent selected from the group consisting of sucrose, trehalose, polyvinyl pyrrolidone, dextran, or any substance or additive that can retain and protect the activity of the therapeutic agent.

In another embodiment, particles formed of one or more substances, alone or in combination with one or more additives, the latter can be selected from, but not limited to, salts, softening agents, dispersing agents, hardening agents, binding agents, plasticizers, lyoprotectant and cryoprotectant agents, surfactants, surface active agents, coating agents, metals, sugars or any pharmaceutical excipient which are known in the art. An excipient, in this instance is a substance or additive. Preferred pharmaceutical excipients are excipients that are pharmaceutically acceptable or "generally recognised as safe" (GRAS).

9. Additives are defined herein as anything that is not defined as a substance. An additive includes any non-substance that can be used to form, promulgate or modify hair and or pores formation. The additive can be used to modify the physical, chemical and or biological properties of a substance thereby facilitating the technical handling, improving the stability of the said substances, it can also affect the mechanical properties of the resulting substance or substances and or influencing the biological response of the said substances. An example to the latter it can act as an enhancer, enhancing the absorption of a biological/ pharmacological active or it can have bio-adhesive properties.

The additive can be any matter and in any physical state (detailed description 7.1). Environmental additives include factors which form , promote, modify or combinations thereof, changes in the physico-chemical properties of the particles (detailed descriptions 3,4 and 5). These environmental additives include, but are not limited to heat, moisture, radiation, pressure , shear forces, magnetic forces, vibration, systems of agitation, stirring, vortexing, centrifuging, masticating, ultra-sound waves or

extruding (according to *US Patent 6,255,359* these environmental additives were reported to be pore size and pore shape modifiers), electrical or any factors or combinations of factors that favour the formation of hairs and / or pores and/or physico-chemical modification(s) as detailed in detailed descriptions 3, 4 and 5. These additives can be included at any stage or stages a) to f) of detailed description 7 of the present invention. In fact any matter and in any physical state as detailed in detailed description 7.1, which is capable of forming or promoting pore and/or hair and combinations thereof as well as causing any deviation in physico-chemical properties from that of the original particle as defined in detailed description 3, 4 and 5. The original particle defined herein is the particle before contacting with the fluid. For instance, heat as an additive promotes faster particle expansion and / or hair growth and / or pore formation.

10 The fluid is defined herein as the medium or combination of mediums in which partial or complete architecturing takes place. Complete architecturing, in this instance, is defined herein as obtaining particles with the physico-chemical properties as detailed in detailed descriptions 3, 4 and 5 for the intended purpose. Partial architecturing is defined herein as obtaining particles with physico-chemical properties (as detailed in detailed description 3, 4 and 5) any where between those of complete architecturing and those of the original particle. The medium(s) of the fluid can be in different states of matter which are not limited to those of detailed description 7.1 or combinations thereof. The fluid can also comprise one or more constituents which can be present in different states of matter which is not limited to those of detailed description 7.1 or combinations thereof. The constituent and medium defined herein is a substance and/or additive. One or more substances and / or additives of the particle can be present as one or more constituents of the fluid before contacting or during contacting. The fluid may also contain substance(s) and / or additive(s) as constituents, which are not present in the particle.

11 Wherein the medium can be one or more substances, one or more additives or combinations thereof.

12 Wherein the fluid itself, can be in different states of matter which is not limited to those of detailed description 7.1 or combinations thereof, or any fluid whereby an interface is formed between the fluid and particle which facilitates particle architecturing.

13 According to detailed description 12, the preferred state of the fluid is in the liquid state.

14 According to detailed description 13, in the case where the fluid is in the liquid state, the fluid can be aqueous or organic liquid and combinations thereof.

15 According to detailed description 14, the mediums of the fluid can have complete miscibility with each other, are totally immiscible with each other or have miscibility anywhere within these limits.

16 According to detailed description 15, it is preferred that the mediums of the fluid are miscible.

17 Wherein one or more constituents of the medium can be soluble in the medium, insoluble in the medium or have a solubility anywhere within these limits.

18 According to detailed description 14, Wherein the medium(s) of the fluid is (are) selected from the group consisting of but, not limited to water, hydrocarbons solvents (saturated, unsaturated, cyclic, acyclic and/or aromatics), mineral spirit , mineral oils or the like, halogenated solvents (fluorinated, chlorinated, brominated, iodated or mixed halogenated) such as methylene chloride and bromide, freons, bromo-chloro-methane, chloroform, carbontetrachloride , or the like , oxygenated solvents such as ketones, ethers , esters, carboxylic acids , aldehydes , alcohols , carbonates, or the like, nitrogen containing solvents such as amines, amides, or the like, sulphur containing hydrocarbon solvents such as sulphoxides , sulfonates or the like or other hetero-atoms containing hydrocarbon solvents, mineral acids such as sulfonic acids, sulfuric acids , phosphoric acids, nitric acids, or the like or any other liquid or combinations of liquids capable of forming/promoting/modifying hairs and / or pores with or without altering the physico-chemical properties of the particles and or hairs according to detailed descriptions 3, 4 and 5.

It will be understood that the liquid may be a ketone and or an alcohol. Wherein a suitable type of ketone is acetone and a suitable alcohol is

ethanol. Preferably the liquid is a non-solvent for the substance. The liquid can be either a solvent or non-solvent for the additive.

19 According to detailed description 7, wherein the particles to be contacted can be pure substance(s), pure additive(s) or combinations thereof.

20 According to detailed description 19, the particles to be contacted are un-processed or processed using any techniques known to the skilled artisan.

20.1 According to detailed description 20, the particle to be contacted, can be processed but the processing is not limited to spray drying , micronisation, granulation, sieving, fractioning, freeze drying, spray freeze drying, spray-chilling, freeze fracturing, emulsion solvent evaporation/extraction, coacervation, extrusion-spheronisation, coating of nonpareil spheres, wet granulation, dry granulation, crystallization, from a solution, a suspension, an emulsion, micro-emulsion, dispersion, slurry, paste, semi-wet particulates, fibrous and the like or any other techniques known at present and those to be invented.

21 According to detailed descriptions 19 and 20, wherein the particle to be contacted can be of any physico-chemical properties according to detailed descriptions 3, 4 and 5, preferably of the required physico-chemical properties according to detailed descriptions 3, 4 and 5, for the intended purpose.

22 According to detailed description 20, wherein the particles to be contacted are obtained by any process forming particles of any shape and preferably, forming spherical shaped particles, and most preferred, forming hollow and spherical shaped particles.

23 According to detailed description 22, wherein the particles to be contacted are preferably produced by spray drying, small particle size with a narrow size distribution is most preferred.

24 According to detailed description 23, herein the term 'particle' refers to particles having a volume median particle size of between about 0.05 and 4000 micrometers.

25 According to detailed description 24, the volume median particle size is the median diameter of the volume weighted size distribution, also referred to as the Dsub.V,50.

26 According to detailed description 23, the term 'particle size' refers to a volume median particle size as determined by conventional particle size measuring techniques known to those skilled in the art, such as, laser diffraction, photon-correlation spectroscopy, sedimentation, field-flow fractionation, disc centrifugation or electrical sensing zone. Laser diffraction is preferred.

27 According to detailed description 7, contacting defined herein, is the process by which the particles and fluid are brought into intimate contact.

28 According to detailed description 27, wherein the fluid is introduced to the particle. The fluid can be introduced at any rate, and in any state of matter (according to detailed description 7.1) in bulk as droplets, mist, spray or combinations thereof. The particle can be static or in motion (in any direction) as the fluid is introduced.

29 According to detailed description 27, wherein the particle is introduced to the fluid. The particle can be introduced at any rate and the fluid can be static or in motion (in any direction) as the particle is introduced.

30 According to detailed descriptions 28 and 29, environmental additives, (as detailed in detailed description 9) can be applied to the fluid or the particle, to be contacted, or both before and / or during and / or after contacting. The phyico-chemical properties of the particle according to detailed descriptions 3, 4 and 5 may change according to the environmental additive. For instance, heat accelerates particle growth, may induce polymorphic transformations, increase the size of pores whilst modifying pore shape, increases the hollow volume of the particle and increase the crystallinity.

31 According to detailed descriptions 28 and 29 non-environmental additive(s) and or substance(s) in any state of matter (as detailed in detailed description 7.1) can further be added to the particle, to be contacted, to the fluid or both, before and / or during and / or after contacting.

32 According to detailed description 27, wherein contacting and architecturing can occur at the point of particle manufacture, for example, spray drying directly into the fluid or architecturing as the substance or additive crystallizes or forms from solution.

33 According to detailed description 27, contacting can take place from 1 microsecond and above. Preferably from 1 microsecond to several hours and most preferably, from 1 micro-second to 30 minutes.